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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/854,326	05/11/2001	Toni Rita Prezant	18810-81401	7808

7590 02/18/2004

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EXAMINER	
CHEN, SIBIN LIN	
ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 02/18/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/854,326	PREZANT ET AL.	
	Examiner	Art Unit	
	Shin-Lin Chen	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12-29-03*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *32-52* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *32-52* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12-29-03 has been entered.

Applicants' amendment filed 12-29-03 has been entered. Claims 1-31 have been canceled. Claims 32-52 have been added. Claims 32-52 are pending and under consideration.

Priority

Applicant's claim for domestic priority under 35 U.S.C. 119(e) and 120 is acknowledged. However, the provisional application 60/031,338 and applications 09/777,422, 09/730,469, 09/687,911, 09/569,956, 08/894,251 and PCT/US97/21463 fail to disclose the nucleotide sequence of SEQ ID No. 63 and the amino acid sequence of SEQ ID No. 64. Thus, the benefits of the provisional application 60/031,338 and applications 09/777,422, 09/730,469, 09/687,911, 09/569,956, 08/894,251 and PCT/US97/21463 have been denied. The effective filing date of the present application is the actual filing date 5-11-01.

Double Patenting

2. Applicant is advised that should claims 40-44 be found allowable, claims 45 and 48-51 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same

thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k). Claim 40 is directed to the mammalian cell produced by the method of claim 32. Claim 45 is directed to a mammalian cell maintained in vitro and said mammalian cell is produced by a method that is identical to the method of claim 32. Thus, claims 40-44 and claims 45 and 48-51 are duplicate claims.

Claim Rejections - 35 USC § 101

3. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 32-52 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific asserted utility or a well established utility.

The specification fails to provide an asserted use that meets the requirement of 35 U.S.C. 101 for producing mammalian cells in vitro in which neoplastic cellular proliferation or transformation, or both, is inhibited or for the mammalian cells that are so produced. There is no specific utility or a well-established utility for the mammalian cells whose neoplastic cellular proliferation or transformation, or both, is inhibited, or for the method of producing said mammalian cells in vitro. The only readily apparent use for the method is to study the effects of the method. The use of an invention as an object of further research or study does not meet the requirement of 35 U.S.C. 101.

Claims 32-52 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 32-52 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for enabling for inhibiting transactivation activity of PTTG1 by nearly half via overexpression of PTTG 2 protein (amino acid residues 1-191 of SEQ ID No. 64) *in vitro*, does not reasonably provide enablement for inhibiting transactivation activity of PTTG1 via overexpression of mutant PTTG 2 lacking 12 C-terminal amino acid residues (residues 180-191 of SEQ ID No. 64) of the PTTG2 protein or overexpression of a mammalian PTTG2 peptide having at least 95% sequence homology with said mutant PTTG2 protein *in vitro*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Claims 32-52 are directed to a method of producing mammalian cells in which neoplastic cellular proliferation or transformation, or both, is inhibited, said method comprising delivering an expression vector to the mammalian cell and said expression vector comprising a promoter and a polynucleotide containing a DNA encoding a mammalian PTTG2 peptide consisting

essentially of a functional fragment comprising at least amino acid residues 1-180 of SEQ ID No. 64 or encoding a mammalian PTTG peptide having at least about 95% sequence homology to said functional fragment, and the mammalian cells produced by said method.

The specification discloses that stable expression of human PTTG1 polypeptide in transfected NIH3T3 cells induces tumor formation *in vitro* and *in vivo*, and the proline-rich domain of PTTG is important for PTTG-mediated neoplastic transformation. Human PTTG2 polypeptide is 90% identical to human PTTG1 polypeptide for 179 amino acid residues and its carboxyl terminal is non-homologous for an additional 12 amino acid residues, and removal of the carboxy terminal segment increases transactivation activity by 26 folds. The specification also discloses that overexpression of PTTG2 inhibits transactivation activity of PTTG1 by nearly half *in vitro* (specification, page 116). The claims encompass inhibiting neoplastic cellular proliferation and/or transformation of a mammalian cell in vitro by delivering a composition comprising any expression vector expressing a mammalian PTTG2 peptide consisting essentially of a functional fragment comprising at least amino acid residues 1-180 of SEQ ID No. 64 or encoding a mammalian PTTG peptide having at least about 95% sequence homology to said functional fragment, and the mammalian cells produced by said delivery of DNA into mammalian cells.

The specification fails to provide adequate guidance and evidence for inhibiting neoplastic cellular proliferation and/or transformation of a mammalian cell in vitro by delivering a composition comprising any expression vector expressing a mammalian PTTG2 peptide consisting essentially of a functional fragment comprising at least amino acid residues 1-180 of

SEQ ID No. 64 or encoding a mammalian PTTG peptide having at least about 95% sequence homology to said functional fragment.

The specification indicates that "the unique C-terminal of PTTG2 is responsible for transactivation inhibition, and a mutant PTTG2 plasmid, encoding a truncated PTTG2 (aa 1-179, confirmed by immunocytofluorescence [not shown]), no longer inhibited PTTG1 transactivation (Figure 32B)" (see page 115 lines 22-25). It appears that the C-terminal (amino acid residues 180-191 of SEQ ID No. 64) is essential for inhibiting transactivation of PTTG1. Therefore, a peptide containing only amino acid residues 1-180 of SEQ ID No. 64 or a mammalian PTTG2 peptide that is at least 95% identical to said peptide would not be able to inhibit transactivation of PTTG1 or to inhibit neoplastic cellular proliferation or transformation in the mammalian cells overexpressing PTTG1 in vitro.

Further, the amino acid sequence of a protein determines its structural and functional properties, and predictability of which amino acids can be removed from a protein's sequence and still result in similar activity is extremely complex, and well outside the realm of routine experimentation, because accurate predictions of a protein's structure from mere sequence data are limited. Rudinger, 1976 (Peptide Hormones, Edited by Parsons, University Park Press, Baltimore, p. 1-7), points out that "The significance of particular amino acids and sequences for different aspects of biological activity cannot be predicted *a priori* but must be determined from case to case by painstaking experimental study" (e.g. p. 6). Kaye et al., 1990 (Proc. Natl. Acad. Sci. USA, Vol. 87, pp. 6922-6926) teaches that "A single amino acid substitution results in a retinoblastoma protein defective in phosphorylation and oncoprotein binding" (e.g. Title). Skolnick et al., 2000 (Trends in Biotech, Vol. 18, p. 34-39) states "Sequence-based methods for

function prediction are inadequate because of the multifunctional nature of proteins. However, just knowing the structure of the protein is also insufficient for prediction of multiple functional sites. Structural descriptors for protein functional sites are crucial for unlocking the secrets in both the sequence and structural-genomics projects" (e.g. abstract). Skolnick further states that "Knowing a protein's structure does not necessarily tell you its function" and "Because proteins can have similar folds but different functions, determining the structure of a protein may or may not tell you something about its function" (e.g. p. 36, box 2). Since the claims encompass adding to or changing within the amino acid residues 1-180 of SEQ ID No. 64, it would be unpredictable at the time of the invention whether a mammalian PTTG2 peptide that is at least 95% identical to amino acid residues 1-180 of SEQ ID NO. 64 would be able to inhibit neoplastic cellular proliferation or transformation in mammalian cells overexpressing PTTG1. In addition, a PTTG2 peptide containing only amino acid residues 1-180 of SEQ ID No. 64 can not inhibit neoplastic cellular proliferation or transformation in mammalian cells overexpressing PTTG1. Thus, one skilled in the art at the time of the invention would not know how to use the claimed expression vector expressing mammalian PTTG2 peptide to inhibit neoplastic cellular proliferation or transformation in mammalian cells overexpressing PTTG1 or to produce mammalian cells in which neoplastic cellular proliferation or transformation, or both, is inhibited.

For the reasons discussed above, it would have required undue experimentation for one skilled in the art at the time of the invention to practice over the full scope of the invention claimed. This is particularly true given the nature of the invention, the state of the prior art, the

breadth of the claims, the amount of experimentation necessary, the working examples provided and scarcity of guidance in the specification, and the unpredictable nature of the art.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (571) 272-0726. The examiner can normally be reached on Monday to Friday from 9:30 am to 6 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson can be reached on (571) 272-0804. The fax phone number for this group is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist, whose telephone number is (703) 308-0196.

slchen

Shin-Lin Chen, Ph.D.